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Usefulness of pharmacy outpatient clinic follow-up for maintaining relative dose intensity in patients on adjuvant CAPOX chemotherapy for gastric cancer

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Abstract. Capecitabine plus oxaliplatin (CAPOX) is a frequently used treatment regimen for colorectal and gastric cancer as postoperative adjuvant chemotherapy. Nausea, vomiting and diarrhea are reported to be the main causes of decreased adherence to CAPOX therapy. The Cancer Institute Hospital, Japanese Foundation for Cancer Research, provides a pharmaceutical outpatient clinic for patients undergoing outpatient chemotherapy. In the present study, dose intensity and severity of side effects of CAPOX therapy as adjuvant chemotherapy after surgery for gastric cancer were evaluated before and after outpatient pharmacy clinic follow-up. This was a retrospective, observational study. Data from consecutive patients who received CAPOX therapy as adjuvant therapy after surgery for gastric cancer from November 2015 to April 2021 were obtained. Two patients were excluded, and 59 patients were included in the analysis. In total, there were 243 prescription recommendations at the pharmacy outpatient clinic. The most common prescription recommendation was prescription of supportive care medications (53.9%, 131 instances), followed by postponement of treatment (10.3%, 25 instances) and dose reduction of each drug (8.2%, 20 instances). The mean relative dose intensity (RDI) was 67.8±20.2% [95% confidence interval (CI), 62.5-73.1%] for capecitabine and 62.2±20.7% (95% CI, 56.9-67.6%) for oxaliplatin. The mean RDI was 72.5±18.8% (95% CI, 61.2-83.7%) before capecitabine dose reduction and 90.4±14.8% (95% CI, 81.4-99.3%) after dose reduction. The pharmacy outpatient clinic maintained RDI and contributed to the continuation of treatment by suggesting supportive care medications and recommending reduction of the dosage of anticancer drugs to the physicians.

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Introduction

The number of patients receiving cancer chemotherapy has increased in parallel with the rise in morbidity and mortality from cancer (1). With the increased use of oral anticancer drugs, advances in supportive care for cancer, and changes in the healthcare environment, chemotherapy has shifted from inpatient to outpatient settings (2,3). However, cancer drug therapy is associated with a wide variety of adverse events that can decrease patients' quality of life and reduce dose intensity. Early intervention by healthcare providers for adverse events is effective in prolonging survival and continuing treatment (4). Collaboration of pharmacists with physicians in providing pharmacological intervention is effective for maintaining quality of life, laboratory testing rates and treatment retention (5-7). Care by the healthcare team is important, and pharmacists provide safe cancer drug therapy within the healthcare team.

Capecitabine plus oxaliplatin (CAPOX) is a frequently used treatment regimen for colorectal and gastric cancer as postoperative adjuvant chemotherapy (8-10). Treatment consists of capecitabine (1,000 mg/m^2 twice daily on days 1-14 of each cycle) and oxaliplatin (130 mg/m^2 intravenously on day 1 of each cycle). Treatment continues for eight 3-week cycles. CAPOX therapy in postoperative adjuvant chemotherapy for gastric cancer has been reported to cause nausea (87% all grades, 10% grade 3/4), peripheral neuropathy (76% all grades, 33% grade 3/4) and hand-foot syndrome (48% all grades) in Japanese patients (10). Maintaining dose intensity is important in postoperative adjuvant chemotherapy, and adherence to capecitabine is important for this purpose. Nausea, vomiting and diarrhea are reported to be the main causes of decreased adherence to CAPOX therapy (11). Since CAPOX therapy is started after gastrectomy in patients with gastric cancer, special attention should be paid to decreased adherence and dose intensity due to gastrointestinal toxicity (10).

Pharmacists are experts in medications, and in recent years, pharmacists have met with patients to assess the severity of side effects (11-13). The Cancer Institute Hospital, Japanese Foundation for Cancer Research, provides a pharmacy outpatient clinic for patients undergoing outpatient chemotherapy (Fig. 1). In The Cancer Institute Hospital, proactive intervention by pharmacists to check for adherence and side effects (which are one cause of nonadherence) is considered necessary, and a pharmacy outpatient clinic is held for patients receiving oral chemotherapy treatment. The main tasks related to CAPOX performed in the pharmacy outpatient clinic are as follows: i) Use of the capecitabine treatment diary to check for capecitabine adherence and leftover medication; ii) provision of prescription support for CAPOX treatment; iii) assessment of side effects; and iv) suggestion of prescriptions for medication as supportive therapy (13). In practice, prescription support for CAPOX treatment consists of a pharmacist recording the CAPOX doses and the administration period required for the next cycle in the electronic medical record (EMR). This is then checked and authorized by a physician to enable the prescription to be issued. If capecitabine is left over from the previous cycle, the amount to be prescribed is adjusted accordingly. There have been reports of a decrease in the rate of inquiries related to capecitabine as a result of pharmacy outpatient clinics, in addition to decreases in emergency visits and emergency hospitalizations (14,15). However, there are no studies of pharmacists designing prescriptions of anticancer drugs for physicians, which contributed to patient care. Therefore, in the present study, dose intensity and severity of side effects of CAPOX therapy as adjuvant chemotherapy after surgery for gastric cancer before and after outpatient pharmacy clinic follow-up were evaluated.

Study design and treatment. This was a retrospective, observational study. Patients with pathological Stage II/III gastric cancer who underwent D2 gastrectomy were included. CAPOX was selected based on the evidence from the CLASSIC trial and in accordance with the institutional treatment protocols approved by the Regimen Review Committee of The Cancer Institute Hospital, which designated CAPOX as a preferred combination therapy for patients at high risk of recurrence during the study period (16). Data were obtained from consecutive patients who received CAPOX treatment as adjuvant therapy for gastric cancer. The CAPOX regimen comprised a 2-h intravenous infusion of oxaliplatin 130 mg/m^2 on day 1, and oral capecitabine at 1,000 mg/m^2 twice daily was given for 14 days on a 3-week cycle. Interviews were held at the pharmacy outpatient clinic between November 1, 2015 and April 30, 2021 at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research using EMRs. The exclusion criterion was limited to patients for whom the RDI could not be calculated accurately due to unknown leftover capecitabine amounts; consequently, two patients were excluded. The Clinical Research Ethics Review Committee of the Japanese Foundation for Cancer Research Cancer Institute Hospital approved the present study (approval no. 2021-GB-017). Following this approval, data for this retrospective analysis were extracted from EMRs between November 2021 and March 2023.

Statistical analysis. All analyses were prespecified based on the study objectives. Given the retrospective, observational design and small sample size, the results are presented primarily using descriptive statistics (mean, percentage, and event counts). Results are presented as the mean ± SD [95% confidence interval (CI)]. The 95% CIs for the mean relative dose intensities (RDIs) were calculated using the standard method for a single sample mean.

No formal hypothesis testing was performed to compare the RDIs or adverse event counts before and after the pharmacist intervention. The comparison of pre- and post-intervention data serves only to show descriptive changes and potential associations, not to establish statistical significance or causality. Statistical analyses were performed using JMP Pro version 14 (SAS Institute Japan).

Pharmacy outpatient clinic and prescription proposals by pharmacists to physicians. In the pharmacy outpatient clinic of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research, pharmacists checked adherence to oral anticancer drugs and assessed side effects, which are one cause of non-adherence, before the patients were examined by their physicians (12,13). In the pharmacy outpatient clinic, pharmacists conducted direct patient interviews and assessments. In particular, the pharmacists played two important roles, confirmation and suggestion. Confirmation involved checking the patients' adherence to capecitabine and evaluating the side effects. Suggestion involved including suggestions in patients' EMRs regarding the most effective prescription for supportive pharmacotherapy, the timing of the next anticancer drug dose, and the administration regimen. Recommendations for prescriptions at the pharmacy outpatient clinic from the second cycle to the end of treatment were assessed. The number of prescription recommendations of medications for supportive care, reuse of leftover capecitabine, postponement of treatment, dose reduction of each drug, and suspension of oxaliplatin were evaluated. The EMR was utilized as a tool for checking patient history, documenting adherence and side effects, and communicating prescription suggestions to physicians. No artificial intelligence was involved in the patient interview or assessment process during the study period.

Number of occurrences of Grade ≥3 non-hematological toxicity before and after pharmacist-suggested prescription of supportive care medications and pharmacist-suggested dose reduction of anticancer drugs. The number of Grade ≥3 non-hematological toxicity events over the treatment period was examined. Adverse events were evaluated based

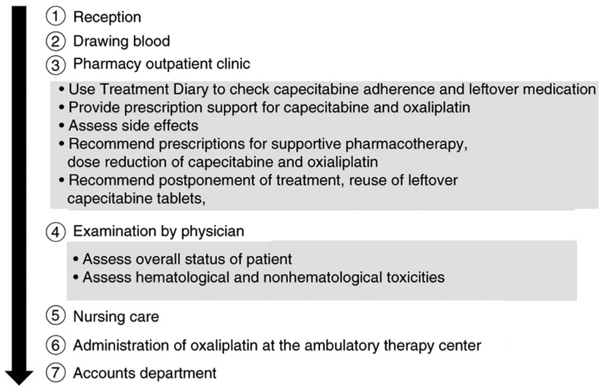

Figure 1. Patient flow and main tasks performed in the pharmacy outpatient clinic with capecitabine plus oxaliplatin treatment.

on pharmacist assessments. Of these, Grade ≥3 non-hematological adverse events for which supportive care medications were proposed and Grade ≥3 non-hematological toxicity in the next course after the proposal were evaluated. Grade ≥3 non-hematological toxicity for which dose reductions of each drug were proposed were also investigated. Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0; https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40).

RDI before and after pharmacist-proposed CAPOX dose reduction. The number of recommendations for dose reduction of CAPOX from the second course to the end of treatment was studied. The RDI was calculated before and after a pharmacist-recommended dose reduction of each drug and subsequent physician-prescribed dose reduction of each drug. The RDI was calculated based on previous studies (10,17,18). In the present study, the RDI was calculated with consideration of treatment delays and dose reductions. RDI (%) was defined as: RDI (%)=(Actual dose intensity/Planned dose intensity) x100.

The planned dose intensity was calculated by dividing the cumulative dose (mg/m^2) that would have been administered if the treatment had been completed without any dose reductions or delays by the planned treatment duration (days). The actual dose intensity was calculated by dividing the actual cumulative dose (mg/m^2) administered by the actual treatment duration (days), including any delays or interruptions. This method reflects the impact of both dose modifications and treatment schedule changes on the overall intensity of chemotherapy. The overall RDI was calculated based on the total planned and actual doses over the entire treatment course, whereas the RDI before and after the dose-reduction recommendation was calculated using the data from only one course prior to and one course following the intervention.

Results

Patients and characteristics. Data were obtained from 61 consecutive patients with gastric cancer. Two patients were excluded from the final analysis due to an unclear number of capecitabine tablets taken, leading to a final total of 59 patients included. Patient characteristic data for the 59 patients analyzed are reported in Table I. The median age was 61 years (range: 23-77 years), and the study included 40 male and 19 female patients. In terms of surgical procedure, 23 (39.0%) underwent total gastrectomy, 33 (55.9%) underwent distal gastrectomy, 1 (1.7%) underwent cardiac gastrectomy, and 2 (3.4%) underwent other procedures. The mean duration of CAPOX treatment was 7.39 cycles (range: 1-8 cycles).

Table I. Clinicopathological characteristics of patients (total n=59).

Clinicopathological characteristics	Number of patients, n (%)
Median age, years (range)	61.0 (23-77)
Sex	
Male	40 (67.8)
Female	19 (32.2)
Eastern Cooperative Oncology Group performance status	
0	30 (50.8)
1	29 (49.2)
Pathological stage	
IIA	4 (6.8)
IIB	29 (49.1)
IIIC	23 (39.0)
Others	3 (5.1)
Surgical procedure	
Total gastrectomy	23 (39.0)
Distal gastrectomy	33 (55.9)
Cardiac gastrectomy	1 (1.7)
Others	2 (3.4)
Duration of use (cycle)	
Mean (SD)	7.39 (1.59)
Range	1-8
Creatinine clearance (ml/min)	
Median (Range)	88.3 (38.4-168.2)

Prescription recommendations at the pharmacy outpatient clinic to physicians. In total, prescription recommendations at the pharmacy outpatient clinic were observed in 243 instances. (Note: 'Instances' refers to the total number of intervention events, including multiple recommendations made for a single patient, reflecting the frequency and workload of pharmacist intervention). The most common prescription recommendation was prescription of supportive medication (53.9%, 131 instances), followed by reuse of the leftover capecitabine tablets (25.5%, 62 instances), postponement of treatment (10.3%, 25 instances), dose reduction of each drug (8.2%, 20 instances) and suspension of oxaliplatin (2.1%, 5 instances) (Fig. 2). Supportive care medications for adverse events were recommended for nausea and vomiting (37.4%, 49 instances), hand-foot syndrome (24.4%, 32 instances), diarrhea (7.6%, 10 instances), peripheral neuropathy (4.6%,6 instances), anorexia (2.3%, 3 instances) and others (23.7%, 31 instances).

Table II. Prescription recommendations for Grade 3≥ non-hematological adverse events by phamacists.

Grade 3≥ non-hematologic toxicities	Number of instances (n=25)	Number of intervention instances	Prescription of supportive medication	Dose reduction of capecitabine	Both recommendations	Others
Hand-foot syndrome	8	8	3	2	2	1
Peripheral neuropathy	8	7	1	0	0	6
Fatigue	3	2	0	1	0	1
Diarrhea	2	0	0	0	0	0
Nausea	1	1	0	0	0	1
Constipation	1	1	0	0	0	1
Others	2	0	0	0	0	0

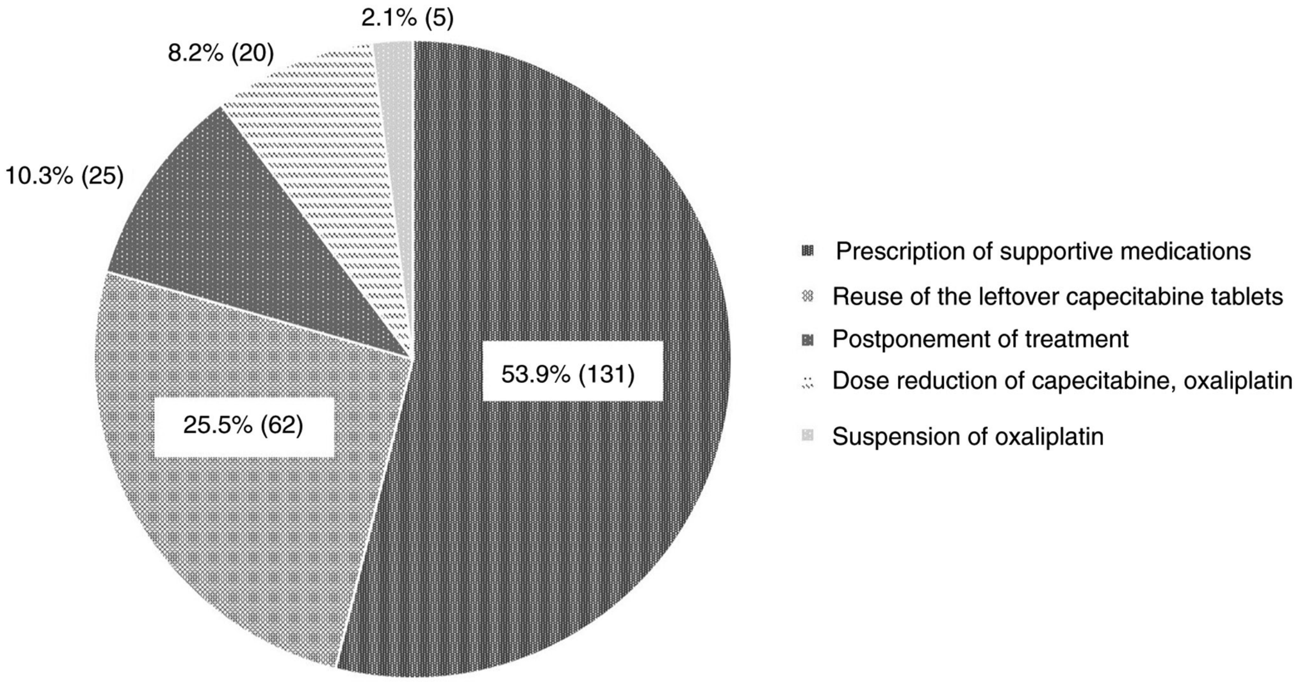

Figure 2. Prescription recommendations details (total events, n=243). Note: n=243 represents the total number of intervention events, including multiple recommendations made for a single patient. Prescription recommendations from pharmacists to physicians during cycles 2-8 and at the end of adjuvant capecitabine plus oxaliplatin therapy.

Grade ≥3 non-hematological adverse events before and after recommended prescriptions for supportive care medication and recommended dose reduction of each drug. In total, Grade ≥3 non-hematological toxicities were observed in 25 instances. The most common Grade ≥3 non-hematological toxicities were hand-foot syndrome (32.0%, 8 instances), peripheral neuropathy (32.0%, 8 instances), fatigue (12.0%, 3 instances), diarrhea (8.0%, 2 instances), nausea (4.0%, 1 instance), constipation (4.0%,1 instance), and others (8.0%, 2 instances) (Table II). Others included oxaliplatin hypersensitivity (4.0%, 1 instance) and gastrointestinal toxicity (4.0%, 1 instance). The number of Grade ≥3 non-hematological toxicities was counted for one treatment course before and one course after the pharmacists' recommendations. This comparison reflects short-term changes in toxicity severity following dose adjustment proposals. However, it does not account for long-term toxicity trends or cumulative effects over the entire treatment duration. Prescription of supportive care medications was recommended for 5 instances of Grade ≥3 hand-foot syndrome and 1 instance of Grade ≥3 peripheral neuropathy. Dose reduction of capecitabine was recommended for 4 instances of Grade ≥3 hand-foot syndrome and 1 instance of Grade ≥3 fatigue. In the next course, after the recommended prescription of supportive care medications, Grade ≥3 hand-foot syndrome decreased to 1 instance. Similarly, after the recommended dose reduction of capecitabine, Grade ≥3 hand-foot syndrome and fatigue were not observed (Table III).

RDI before and after dose reduction of each drug. All 14 recommendations for capecitabine dose reduction by pharmacists were reflected in the physicians' prescriptions for dose reduction. The mean RDI was 72.5±18.8% [95% confidence interval (CI), 61.2-83.7%] before capecitabine dose reduction and 90.4±14.8% (95% CI, 81.4-99.3%) after dose reduction.

Table III. The number of Grade ≥3 non-hematological adverse events before and after pharmacist's recommendations.

	Number of Grade ≥3 non-hematological toxicities	
Intervention	Pre-recommended	Post-recommended
Recommended prescription of supportive medication		
Hand-foot syndrome	5	1
Peripheral neuropathy	1	1
Fatigue	0	0
Subtotal	6	2
Recommended dose reduction of capecitabine		
Hand-foot syndrome	4	0
Peripheral neuropathy	0	0
Fatigue	1	0
Subtotal	5	0

Among the 14 cases with proposed capecitabine dose reduction, treatment delays occurred in 9 cases before the proposal and 3 after, and the number of patients unable to receive the medication during the treatment period was 5 before and 2 after. Of 6 recommendations for oxaliplatin dose reduction by pharmacists, 5 recommendations for oxaliplatin dose reduction were reflected in the physicians' prescriptions for dose reduction. The mean RDI was 83.8% (95% CI, 56.7-111.0%) before oxaliplatin dose reduction and 73.8% (95% CI, 62.5-85.1%) after dose reduction. The relative dose intensities of CAPOX were counted one course each before and after the pharmacists' recommendations. This analysis is limited to a short-term comparison and does not reflect maintenance of the overall RDI over the entire treatment duration. For the RDI comparison before and after the dose reduction recommendation, the RDI was calculated for one treatment course each. The mean overall RDI was 67.8±20.2% (95% CI, 62.5-73.1%) for capecitabine and 62.2±20.7% (95% CI, 56.9-67.6%) for oxaliplatin.

Discussion

In the present study, the RDI and severity of side effects of CAPOX therapy as adjuvant chemotherapy after surgery for gastric cancer before and after pharmacy outpatient clinic follow-up of patients were investigated. Examining the number of adverse events before and after the pharmacist suggested prescriptions, pharmacological intervention at the pharmacy outpatient clinic had an impact on decreasing the severity of adverse events. In particular, the suggestion of supportive care medications and capecitabine reduction for Grade 3 or higher hand-foot syndrome was effective in reducing the severity of severe symptoms. Therefore, pharmacists working with physicians to provide pharmacological interventions can manage adverse events appropriately in patients. It was also evident that the pharmacy outpatient clinic led to maintenance of RDI.

In the present study, there were various types of prescribing suggestions in the pharmacy outpatient clinic for the physicians. The highest percentage of suggestions made by pharmacists were for supportive care medications (53.9%, 131 instances). This result was consistent with previous studies (7,19). Supportive care medications for nausea and vomiting were the most frequently suggested, at 37.4%. Chemotherapy-induced nausea and vomiting are side effects that significantly affect patients undergoing outpatient cancer chemotherapy (20). Significant improvements in quality of life have been demonstrated after pharmacological intervention for nausea and vomiting (5). The pharmacists may have contributed to the maintenance of RDI by assessing the patients' conditions and suggesting appropriate supportive care medications for nausea and vomiting. Dose reduction suggestions for anticancer drugs accounted for 8.2% (20 instances). This may have provided favorable support for peripheral neuropathy, for which there is no supportive care medication of known benefit.

Outpatient pharmacological interventions focused on supportive care medication suggestions for Grade 3 or higher non-hematological toxicities and suggested reductions in anticancer drugs. Before and after the proposed supportive care, the number of Grade ≥3 hand-foot syndrome instances decreased from 5 to 1. This assessment was limited to a comparison between one treatment course prior to and one course following the intervention, and the reduction in Grade severity cannot exclude the possibility of improvement due to the natural course of the condition. However, peripheral neuropathy remained at one instance and did not improve. The pharmacists' suggestions for supportive care medications decreased the severity of hand-foot syndrome, but not the severity of peripheral neuropathy. Hand-foot syndrome improves with drug withdrawal, but peripheral neuropathy is a cumulative condition and does not improve rapidly, and no drug has clearly demonstrated benefit for peripheral neuropathy. It has been reported that the implementation of a pharmacy outpatient clinic for peripheral neuropathy significantly improved patient quality of life, but there was no significant difference in the occurrence of Grade ≥2 peripheral neuropathy (5). It was also reported that supportive care medications were primarily suggested for peripheral neuropathy, and that anticancer drug dose reductions were suggested for 11.1% of prescriptions proposed (5). In the present study, the lack of improvement in the severity of peripheral neuropathy may be due to the fact that the authors did not propose a reduction in the dose of anticancer drugs for Grade 3 or higher peripheral neuropathy. The proposed capecitabine dose reduction for 5 instances of Grade 3 or higher hand-foot syndrome was reduced to 1 instance of Grade 3 or higher hand-foot syndrome. Given this, when pharmacists collaborate with physicians in cancer drug therapy, the severity of side effects is reduced.

Pharmacists have an important role in the management of adverse effects of chemotherapy. Pharmacists are not only responsible for dispensing medications and providing medication guidance, but also for interviewing patients and collaborating with physicians to manage adverse drug reactions. Pharmacist care has also been reported to improve treatment of patients with HIV, and the present study also showed results demonstrating direct benefit for patients through pharmacist care (21).

The RDI for patients for whom pharmacy outpatient clinic follow-up was provided was studied. CAPOX had mean RDIs of 67.8 and 62.2%, respectively. The reported RDI for capecitabine was 67.2% in a previous study, which is almost the same as in the present study (67.8 vs. 67.2%) (10). The results may indicate that the dose intensity for capecitabine was maintained through the implementation of the pharmaceutical outpatient clinic. However, the reported RDI for oxaliplatin was lower in the present study than that reported in the aforementioned previous study (62.2 vs. 73.4%) (10). This may be due to the fact that the RDI in the present study was calculated taking into consideration the duration of treatment. The RDI for oxaliplatin may also be due to its susceptibility to dose reduction or treatment deferral due to adverse events. The contrasting trends in RDI following dose reduction for the two drugs warrant further discussion. The observed increase in capecitabine RDI from 72.5 to 90.4% after dose-reduction suggestions may be attributed to improved treatment continuity. Specifically, dose reduction likely alleviated severe adverse events, thereby reducing the frequency of subsequent treatment delays or interruptions. Since the RDI is calculated based on the dose per unit time, the reduction in delays resulted in an overall higher dose intensity per day. Conversely, the decrease in the oxaliplatin RDI from 83.8 to 73.8% after dose reduction suggests a different mechanism. This drop is likely due to the nature of its major dose-limiting toxicity, peripheral neuropathy. Since peripheral neuropathy is a cumulative condition, dose reduction often fails to prevent subsequent treatment deferrals or extensions of treatment duration. Since the RDI calculation strictly accounts for the actual treatment duration (days), the extended treatment time due to the persistent cumulative toxicity resulted in a relatively lower overall dose intensity per unit time. This distinction highlights that, though capecitabine dose optimization aids acute toxicity management and schedule maintenance, oxaliplatin's cumulative toxicity can negate the positive RDI impact of dose reduction. In the CLASSIC trial, a minimum of 6 cycles of either capecitabine or oxaliplatin was found to be important for the efficacy of adjuvant chemotherapy (16). Therefore, it is important to continue administration with appropriate dose modification. In the present study, pharmacist prescribing suggestions reduced the severity of adverse events and maintained the RDI for capecitabine. Therefore, pharmacological intervention by a pharmacist is necessary to maintain RDI.

The impact of the pharmacists' suggestions for capecitabine dose reduction on the RDI was examined. In the present study, proposals for dose reduction of anticancer drugs by pharmacists included 14 instances for capecitabine and 5 instances for oxaliplatin. After the pharmacist suggested a reduced dose of the anticancer drug and the physician implemented the dose adjustment, the mean RDI for capecitabine increased from 72.5 to 90.4%. Specifically, the reduction in treatment delays (from 9 to 3 cases) and interruptions (from 5 to 2 cases) following dose optimization directly contributed to the increased RDI. These findings suggest that appropriate dose reduction to alleviate adverse events can improve treatment continuity, which is more effective for sustaining dose intensity than attempting to maintain a higher dose that leads to frequent treatment cessations. These results indicate that pharmacists' suggestions for reducing the dose of anticancer drugs are useful for maintaining the RDI. Regarding the choice of postoperative adjuvant chemotherapy, the JACCRO GC-07 trial recently established the efficacy of S-1 plus docetaxel (DS) for Stage III gastric cancer, demonstrating superior outcomes compared with S-1 monotherapy. While the present study focused on the CAPOX regimen, the clinical significance and pharmacist-led management of DS therapy are also considered important areas for future investigation and comparative analysis (17). It has been reported that interprofessional collaboration between clinical pharmacists and physicians in the outpatient setting is necessary, and without collaboration in the form of adverse event interventions, prescription suggestions, and patient education, as in the present study, no results will accrue directly to patients (22).

The present study has several limitations. Because it focused on postoperative CAPOX therapy for gastric cancer and evaluated RDI retrospectively, it was not possible to compare the pharmacy outpatient clinic follow-up group with a non-pharmacy outpatient clinic follow-up group. Therefore, it is not clear whether maintenance of the RDI is due to the implementation of pharmacy outpatient clinic follow-up. The absence of a control group makes it difficult to determine whether pharmacist intervention truly affects the RDI and survival indicators such as disease-free survival (DFS) and overall survival (OS), which limits the clinical translatability of the findings. Efficacy and survival indicators were not assessed primarily because this was a retrospective, observational study with the main objective of evaluating the impact of pharmacist intervention on RDI maintenance and adverse event management. The study's design, characterized by the absence of a control group and a small sample size, made it statistically inappropriate to draw robust conclusions regarding long-term clinical outcomes such as DFS or OS. Future studies should consider incorporating a control group design, ideally consisting of patients who do not receive follow-up in the dedicated pharmacist outpatient clinic. In addition, survival time analyses such as disease-free survival and overall survival were not performed. Although the pharmacists' prescribing suggestions reduced the severity of Grade 3 or higher non-hematological toxicities, improvement in quality of life could not be assessed. Furthermore, the comparison of RDI values with historical data was exploratory and cannot exclude the influence of confounding factors such as differences in patient background characteristics or advances in medical care (10). Finally, the small sample size (n=59) from a single institution and the lack of stratification by surgical method (total/partial gastrectomy) or age significantly limit the generalizability of the findings, particularly to high-risk groups such as patients following total gastrectomy. Furthermore, performing a robust sensitivity analysis (for example, excluding patients with early treatment completion) was not feasible due to the small, single-center, retrospective nature of the study, since such exclusions would have rendered the remaining sample size insufficient for meaningful analysis. This represents another constraint on the generalizability of the present findings. In addition, the relationship between the RDI and long-term outcomes such as DFS or OS was not assessed. Given that the average RDI in the present cohort was below the 80% threshold associated with survival benefits in previous studies, the clinical relevance of RDI maintenance in this context remains unclear.

In conclusion, the usefulness of pharmacy outpatient clinic follow-up was evaluated based on the RDI. Although this study did not include a control group, pharmacist outpatient follow-up may have contributed to maintenance of the RDI and the continuation of treatment by suggesting supportive care medications and dosage reductions of anticancer drugs to the physician.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

MN, TY, KKa, HS, DT and KS conceived the study, participated in its design and coordination, and performed statistical analyses and interpretation. MN, TY, KKa, YK, KKo, TA, WS and MH performed data curation. DT, MO, KC, TW, KY and MY contributed to the study design, provided critical intellectual input, and supervised the research. MN, TY, KKa and YK drafted the manuscript. All authors read and approved the final version of the manuscript. MN, TY, KKa and YK confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was approved by Clinical Research Ethics Review Committee of the Japanese Foundation for Cancer Research Cancer Institute Hospital (approval no. 2021-GB-017; Tokyo, Japan). The use of the opt-out method in lieu of written, informed consent was approved by the Clinical Research Ethics Review Committee of the hospital.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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